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1.3 5-TRINEOPENTYLBENZENES

A Nuclear Magnetic Resonance Study of Chemical Exchange

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1973



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To

Gunnel and Mattias

AB Lunda-Kopia

LIST OF SYMBOLS AND THEIR MEANINGS

$\omega_A - \omega_B$	chemical shift difference (rad. s^{-1}) between two nuclei A and B; ω_A and ω_B are the Larmor frequencies of nuclei A and B, respectively
δ	shift parameter defined as $2 \delta = \omega_A - \omega_B$
J_{AB}	coupling constant between two nuclei (i.e. protons) A and B
AB	If the chemical shift difference between two nuclear resonances is of the same order of magnitude as the coupling constant, they are said to constitute an AB spectrum; the symbolization A_2 is used when two nuclei are magnetically equivalent.
ψ	a general symbolization of a wave function including electron and nuclear position, electron and nuclear spins
c_i	coefficients in the expanded wave function
ϕ_i	normalized wave functions
α, β	nuclear spin functions
$\alpha\alpha, \alpha\beta, \beta\alpha, \beta\beta$	basis functions for a set of two nuclei
B_0	the static magnetic field (usually defined to be in the z-direction)
B_1	the stimulating rf field (usually defined to be in the x-direction)
γ_i	the gyromagnetic ratio of nucleus i

ω_1	frequency of the rf field (related to B_1 by $\omega_1 = \gamma B_1$)
$\mathcal{H}$	Hamilton operator; the form of this operator for an AB system is $\mathcal{H} = \omega_A \hat{I}_z^A + \omega_B \hat{I}_z^B + J_{AB} \cdot \hat{I}^A \cdot \hat{I}^B$ where $\hat{I}$ is the spin angular momentum operator. (B_0 is in the negative z-direction.)
ρ	density operator
Tr	trace of a matrix (the sum of all diagonal components)
ρ^0	the density operator at thermal equilibrium; a general expression for this operator is $\rho^0 = \exp(-\mathcal{H}/kT) / \text{Tr} \exp(-\mathcal{H}/kT)$
ρ_{ij}	the ij matrix element of the density operator
$[\rho, \mathcal{H}]$	the commutator between the density operator and the Hamiltonian, defined as $\rho\mathcal{H} - \mathcal{H}\rho$
T_1	spin-lattice or longitudinal relaxation time
T_2	spin-spin or transverse relaxation time
τ	mean lifetime for a magnetic nucleus in a given site

Molecular conformations¹ are of primary importance in determinations and interpretations of reactivity in chemical reactions. To a large extent the stability of a conformer is governed by attractive and repulsive non-bonded interactions, and in some cases also by existing electronic delocalizations between atoms or groups of atoms within the molecule in question. A rotation of one part of a molecule with respect to another part about a chemical bond is usually accompanied by a change in the potential energy of the molecule. In some molecules internal rotation of this kind gives rise to the phenomenon of rotational isomerism, in which the "molecules" exist as an equilibrium mixture of two or more conformers. A study of a restricted rotation of this kind about single or partial double bonds can thus provide insight into factors influencing the height of the energy barrier for an interconversion process, as well as the energy difference between the conformers involved.

Many different methods have been utilized for such studies, and in general the magnitude of the energy barrier determines the method to be used. Among organic chemists there has been a special interest in NMR (nuclear magnetic resonance) kinetic studies during the last two decades. A major reason for the increased activity in this area is certainly the great amount of information concerning both reaction mechanisms and molecular conformation that can be gained by this method in a rather easy way. (For comprehensive reviews of the subject and its application, see ref. 2-4.)

After the initial preparation of the 1,3,5-trineopentylbenzene system^{5,6} and some derivatives⁷ in 1969, it soon became apparent that these molecules were amenable to NMR kinetic and conformational studies. Questions of interest in this context were:

- a. Are the rotations of the neopentyl groups independent of each other or are they for instance coupled to each other in a concerted rotation of the groups?
- b. Which conformers (arrangements in space of neopentyl groups) exist at a given temperature? In what way is the stability of these conformers dependent on the substituents in the aromatic ring?

In the course of this study it was found that there was a unique opportunity to utilize rotational barriers determined by one and the same physical method as a quantitative measure of the "size" of ring substituents (H, F, Cl, Br, I and CH₃).

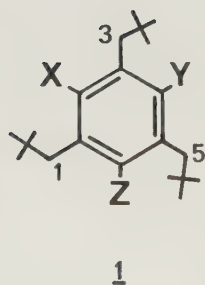
The work to be summarized in this thesis describes ¹H and ¹³C NMR studies of some mono-, di- and tri-substituted 1,3,5-trineopentylbenzenes, and concerns problems of the kind mentioned above. The papers describing the work in detail are given below and are in the following referred to by their Roman numerals.

- I. Bertil Nilsson, Robert E. Carter, Kjell-Ivar Dahlqvist and József Márton, Barriers to Internal Rotation in 1,3,5-Trineopentylbenzenes-II. Unsymmetrically Halogen-Substituted Compounds., Org.Magn.Res., 4, 95 (1972).
- II. Bertil Nilsson, Per Martinson, Kåre Olsson and Robert E. Carter, Barriers to Internal Rotation in Trineopentylbenzenes-III. Nitro- Substituted Compounds., J.Am.Chem.Soc., 95, 5615 (1973).
- III. Bertil Nilsson, Barriers to Internal Rotation in Trineopentylbenzenes-IV. A Nuclear Magnetic Double Resonance Study of Chemical Exchange Among Three Spin Coupled Sites., Mol Phys., in press.
- IV. Bertil Nilsson and Torbjörn Drakenberg, Barriers to Internal Rotation in 1,3,5-Trineopentylbenzenes-V. Conformational Studies by Carbon-13 Magnetic Resonance., Org.Magn.Res., in press.

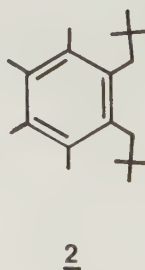
- V. Bertil Nilsson, Per Martinson, Kåre Olsson and Robert E. Carter, Barriers to Internal Rotation in 1,3,5-Trineopentylbenzenes-VI. Correlation Between Barriers to Internal Rotation ($\Delta G^\ddagger$) and Substituent Size., submitted to J. Am. Chem. Soc.

INTERPRETATION OF NMR SPECTRA IN SUBSTITUTED 1,3,5-TRINEOPENTYLBENZENES

In connection with work on the identification of some halogenated 1,3,5-trineopentylbenzenes, Márton and Martinson⁷ discovered that the NMR spectrum of the 1- and 5-methylene protons in 2,4-dibromo-1,3,5-trineopentylbenzene (1b) was composed of an anomalously broad band at probe temperature, which could be due to hindered rotation.



	X	Y	Z
a.	Cl	Cl	H
b.	Br	Br	H
c.	I	I	H
d.	Cl	I	H
e.	Br	I	H
f.	Cl	Br	H
g.	F	Cl	H
h.	CH ₃	CH ₃	H
i.	CH ₃	Br	H
j.	NO ₂	NO ₂	H
k.	NO ₂	Br	H
l.	NO ₂	I	H
m.	[†] Br	Br	NO ₂
n.	[†] Br	Br	Br
o.	[†] Br	I	NO ₂



Later Carter et al.⁸ verified this proposal and examined the methylene proton spectrum by the complete line-shape technique. The observation that the line-shape of the 1- and 5-methylene proton signals is temperature-dependent was suggested to be due to a concerted rotation of the corresponding neopentyl groups, with these groups always as far as possible from each other. The 3-neopentyl group was tacitly

[†] According to the IUPAC rules the neopentyl groups are numbered 2, 4 and 6 in this compound.

assumed to "take care of itself".⁹ The explanation for the rotation of the 1- and 5-neopentyl groups is in form similar to that given by Dix, Fraenkel, Karnes and Newman¹⁰ in their studies of the methylene proton spectrum of 1,2,3,4-tetramethyl-5,6-dineopentylbenzene (2). In the studies⁸ of the symmetrically substituted compounds 1a and 1b no exchange broadening of the 3-methylene signal (between the halogens) could be observed. Clearly, a way of obtaining information from this group would be a study of a dissymmetrically substituted compound, and we thus found it of interest to investigate the three compounds 1d, e and f.

At low temperature ($\sim -30^{\circ}\text{C}$), these compounds gave rise to one AB spectrum for each methylene group and the three rate constants (one for each methylene subspectrum), which could be obtained at higher temperatures, were found to be approximately the same at a given temperature (paper I). In principle, the explanation in terms of simultaneous rotations of all neopentyl groups could be valid for all of these compounds (1a-b, d-f), but model studies reveal that it would imply a very high transition state energy and it would not explain the complicated methylene proton spectrum (220 MHz,¹¹ see figure 1) shown by 1o at reasonably low temperatures. (compare 1o with 1e, where an aromatic proton has been replaced by a a-NO_2 group). The approximately equal rate constants indicate another explanation¹² in terms of induced magnetic nonequivalence in the 1- and 5-methylene protons by the slowly rotating 3-neopentyl group. This means that the 3-neopentyl group creates an asymmetry in the molecule which is transmitted to the rapidly rotating 1- and 5-methylene protons. In each of these methylene groups, the protons feel slightly different magnetic environments and change places when the neopentyl group between the halogens passes π radians back and forth. (For a detailed definition of magnetically equivalent or nonequivalent nuclei, see ref. 13 or 14). An interesting conclusion drawn from this explanation is that even if the slowly rotating neopentyl group is situated in a symmetric environment, as is the case in the dichloro (1a) or dibromo (1b) compounds, it is possible to obtain information about its behaviour.

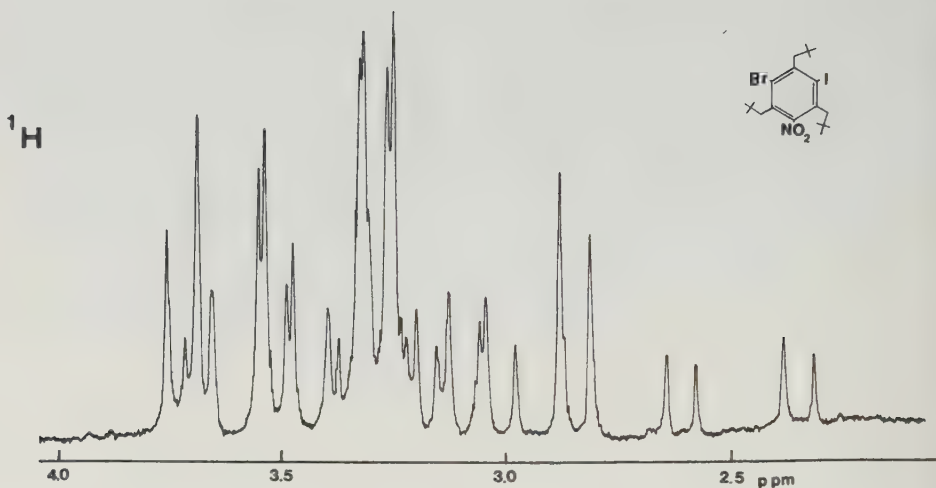
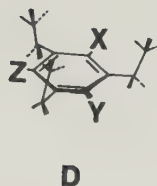
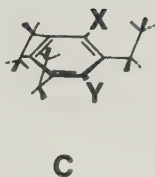
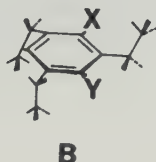
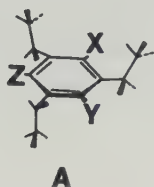


Fig. 1. 220 MHz low temperature NMR spectrum of the methylene protons in 1-bromo-3-iodo-2,4,6-trineopentyl-5-nitrobenzene (1o).

The explanation given by Carter et al.⁸ can be ruled out by studying a molecule in which the rotations of all neopentyl groups are really expected to be slow at a sufficiently low temperature. Of course, the dihalo compounds 1a and 1b or the parent compound (1,3,5-trineopentylbenzene) could be chosen for a dynamic NMR investigation in a temperature range where the passage of an aromatic proton by a neopentyl group is moderately fast, but at that time it was thought that the energy barrier ($\Delta H^\ddagger$), to a large extent caused by an increased proton-neopentyl interaction, was out of the range of the applicability of the NMR technique. (See, however, the discussion of barrier heights below or in paper V). To avoid extremely low temperatures, we have instead chosen to investigate the 4- and 6-methylene proton spectrum of the 1,3-dibromo-2,4,6-trineopentyl-5-nitrobenzene compound (1m), which at $\sim -30^\circ\text{C}$ showed three well-resolved AB patterns at 100 MHz, one with a lower intensity than the other two (papers II and III). At higher temperatures ($\sim +20^\circ\text{C}$), the spectrum appeared as a broad

AB spectrum, which upon raising the temperature further gave rise to a singlet. The changes in these spectra could be interpreted on the basis of the existence of three rotamers (see below; $X=Y=Br$, $Z=NO_2$),



where two are related to each other by symmetry (A and C). The remaining rotamer was depicted to be B (paper II and III), but in principle it might also be the rotamer in which all neopentyl groups are situated on the same side of the aromatic ring (D). Results from a rough estimate of the energy difference between these two rotamers by means of semi-empirical calculations (paper II) indicated that rotamer B is more stable than D, which is also intuitively expected. The difference was however only 0.6 kcal/mol. To convince ourselves that signals in the proton spectra of compound Im are not hidden, we also investigated its ^{13}C -NMR spectrum ($\sim -25^{\circ}C$; proton noise-decoupled) where changes in magnetic environment¹⁵ generally are easier to detect than in 1H -NMR spectra. No evidence for the presence of more than three rotamers could be found (paper IV), and we thus concluded that the population of rotamer D in the dibromonitro compound was too low to be detected by the NMR technique. In contrast, the low temperature carbon-13 NMR spectrum of the quaternary carbons of the

t-butyl groups in the highly symmetric tribromo compound (1n) revealed the existence of two different rotamers, A ($\equiv$ B and C) and D.

The ^1H -NMR spectrum (100 MHz)¹⁶ of the methylene protons in 1n at -19.4°C was poorly resolved (see figure 2a) but the features of the spectrum did indicate the presence of different rotamers. On the

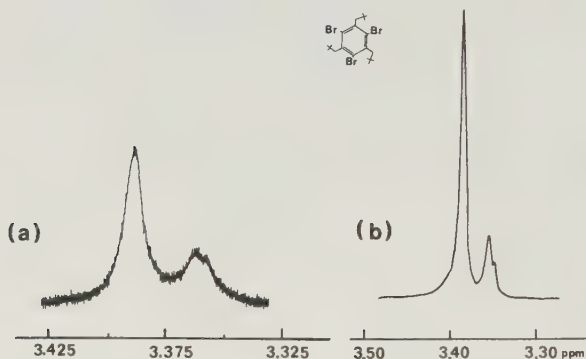


Fig. 2. Methylene proton spectrum of 1,3,5-tribromo-2,4,6-trineopentylbenzene (1n) run at low temperature; (a) 100 MHz, (b) 300 MHz.

basis of the conclusions drawn from the dibromonitro compound (1m) we expected the population of rotamer D in 1n to be smaller than that of rotamer A (see paper IV) and, to begin with, we assigned the most upfield singlet (at 3.357 ppm) in the proton spectrum to the methylene protons in rotamer D. Consequently, the remaining signals refer to methylene protons in rotamers of type A, which theoretically are expected to appear as one AB quartet and one singlet. However, no resolved AB pattern could be observed in the spectrum, which may be due to accidental shift equivalence.¹³ From a statistical point of view it is also expected that the methylene proton signals due to rotamer A would be in the ratio 1:2. In the attempts to computer-

simulate the spectrum at -19.4°C under these conditions, it was found that good agreement between theoretical and experimental spectra could be obtained only if we assumed the two methylene proton singlets of rotamer A to be different in line width. This is perhaps unexpected but it was the only way in which reasonably good spectra-fitting could be obtained with the presumed assignment of signals.

The kind co-operation of Dr. J.S. Shoolery, Varian Associates, made it possible to obtain a low temperature methylene proton spectrum of compound I run at 300 MHz (see figure 2b) with a somewhat better resolution of signals. From this spectrum it seems more reasonable to assume that the two singlets most upfield refer to methylene protons in rotamers of type A. Integration of the signals showed that the area of the most downfield peak was 5.5 times greater than those of the remaining singlets together (the high field peaks appear to be in the ratio 1:2). Surprisingly, this would imply a much larger population of rotamer D than of rotamer A. Support for the assignment is that the spectrum of the quaternary carbons in the t-butyl groups of this compound (paper IV) most likely also can be interpreted on the basis of the assumed existence of an unexpectedly stable rotamer different from A.

We have up to now no convincing explanation for these results, but it is of interest to note that a calculation of the geometry of rotamer D based on idealized bond lengths and angles reveals that the distances between the methyls in the t-butyl moieties of the neopentyl groups are of similar order of magnitude as twice the value for the van der Waals radius of a methyl group ($2 \times 2.0 \text{ \AA}$).¹⁷ Consequently, attractive forces may be of importance. The methyls of the t-butyl groups were treated as extended atoms¹⁸ and we assumed a rigid conformation in which one methyl group from each neopentyl group was symmetrically oriented towards a symmetry axis perpendicular to the aromatic ring. The calculated distance between two methyl groups was $3.4 \text{ \AA}$, but it is realistic to assume that the actual distance will be greater if possible bond bendings are taken into account.

The results from the spectra of the tribromo compound (1n) may also influence the assignment of the AB subspectrum of lower intensity in the dibromonitro compound (1m) in a correct way (see above), but as long as both rotamers (B and D) can not be detected, we do not know which of them is most stable.

Whatever the magnitude of the populations of the different rotamers may be, we can predict the features of a methylene proton spectrum at slow interconversion rates of compounds of type 1 where $X \neq Y \neq Z$ (appropriate X, Y, Z nuclear resonances decoupled) to appear as at most 12 AB patterns. The complex nature of the spectrum of 1o, reproduced above, is thus well understood. With stepwise increase in symmetry ($X \neq Y \neq Z \rightarrow X \neq Y = Z \rightarrow X = Y = Z$) some AB spectra will be shift degenerate and some of them go to A_2 spectra. Of importance for the pattern of the spectrum is of course the relative "effective sizes" of X, Y and Z. If one substituent is so small in comparison with the other two that the mean lifetime on either side of the ring plane of those neopentyl groups situated ortho to the substituent is too short to be detected by NMR, the spectrum is only determined by the interconversion rate of one neopentyl group. One or at most three AB spectra for the methylene protons in such compounds is expected (papers I, II and V).

In view of all these results it is appropriate to note that the rotations of the neopentyl groups in compound 2, mentioned at the beginning, are most probably not concerted. This would imply a rather high energy state if we with concertedness mean equal absolute changes in rotational angles, allowing for example both neopentyl groups to pass methyl groups simultaneously. Moreover, there may be certain similarities in the rotation of one neopentyl group in this compound if comparisons are made with the rotation of the 3-neopentyl group in 2,4-dimethyl-1,3,5-trineopentylbenzene (1h). This would then be reflected in the heights of the barriers of the two compounds and, indeed, the $\Delta H^\ddagger$ value for compound 2 is obviously not twice that for

compound 1h ($\Delta H_{1h}^{\ddagger}=15.3 \pm 0.2$ and $\Delta H_2^{\ddagger}=12.9 \pm 0.6$ kcal/mol). In paper V we have discussed the consequence of a non-concerted rotation of the neopentyl groups in 2, which implies taking into account the possible existence of a highly strained rotamer with both neopentyl groups on the same side of the benzene ring. However, no evidence for the presence of more than one rotamer (paper V) could be found from proton-decoupled ^{13}C -NMR spectra at low temperatures ($\sim -25^\circ\text{C}$). This negative result does not exclude the explanation in terms of non-concerted rotations; it only indicates that the energy difference (ΔG°) between the two conformers is at least 2.0 kcal/mol at -25°C as calculated from a lower limit of 1.5 % of the nondetectable rotamer via the estimation of the signal/noise ratio in the carbon-13 spectrum.

Another consequence of non-concerted rotations is the difficulty in establishing the conformation of highest energy (transition state) for the rotation of one neopentyl group. I will discuss this below in connection with the discussion of entropies of activation.

EVALUATION OF RATE CONSTANTS

In NMR studies of reversible interconversions between two or more conformers there may be profound changes in the shape of the NMR bands if the rate constant(s) characterizing the process is(are) of the same order of magnitude as the frequency separation of the signals from the exchanging nuclei. This implies that there exists an upper limit where the interconversion rate is considerably greater than the separation between the peaks and, consequently, details about the interconversion process are impossible to obtain by this technique. However, with rate constants approximately in the range $0.1\text{--}10^4 \text{ sec}^{-1}$ the characteristic changes in line-shape can give valuable information about the interconversion process as well as about the thermodynamic stability of the "molecules" involved. In the following, I will briefly present the theoretical derivation of equations describing

exchange-broadened NMR spectra and discuss their application to two experimentally different techniques.

Theory

The theory of exchange was first developed by Gutowsky et al.¹⁹ and was later simplified by McConnell.²⁰ These classical equations are most useful in describing line-shapes of first order spectra. To describe more complicated spectra where the exchanging nuclei are also spin-coupled to each other, a new method based on the self-consistent average density matrix²¹ was introduced by Kaplan^{22,23} and was further developed by Alexander,²⁴ Newmark and Sederholm²⁵ and by Johnson.²⁶ The usefulness of the density matrix formalism, which of course is not limited to NMR problems, perhaps needs some comments.

In the application of quantum mechanics, one is primarily interested in expectation values of a physical quantity and, apparently, the knowledge of the complete wave function, $\psi = \sum_i c_i \phi_i$, is not a necessary prerequisite. All information about the system is instead collected in the products of the coefficients $c_i^* c_j$. (The asterisk denotes the complex conjugate.) Consider the expectation value for a physical quantity such as the magnetization, which is represented by the operator $\vec{M}^{op} = \sum_{p=1}^N \gamma \vec{I}_p$. $\vec{I}$ is the spin vector operator and p is the summation index over all the N spin systems. For simplicity, we assume that there is only one type of nuclei. The expectation value of $\vec{I}$ is now given by:

$$\langle \vec{I} \rangle = \langle \sum_i c_i \phi_i | \vec{I} | \sum_j c_j \phi_j \rangle = \sum_{i,j} c_i^* c_j \langle \phi_i | \vec{I} | \phi_j \rangle \quad (1)$$

In the NMR experiment we obtain information about an ensemble of nuclei. The expression in equation (1) is valid for one spin system and, consequently, an average value over all subsystems $\langle \vec{I} \rangle$ must be calculated (see equation (2)).

$$\langle \vec{I} \rangle = \sum_{i,j} \overline{c_i^* c_j} \langle \phi_i | \vec{I} | \phi_j \rangle \quad (2)$$

Note that $\langle \phi_i | \vec{I} | \phi_j \rangle$ is the same for each spin system.²⁷ By introducing an operator ρ in the form $\langle \phi_j | \rho | \phi_i \rangle = \overline{c_i^* c_j}$ equation (2) can be written:

$$\langle \vec{I} \rangle = \sum_{i,j} \langle \phi_j | \rho | \phi_i \rangle \langle \phi_i | \vec{I} | \phi_j \rangle = \text{Tr}(\rho \vec{I}) \quad (3)$$

ρ , which is called the density operator, contains in principle the same information as the wave function and $\text{Tr } \rho = 1$ corresponds to the normalization criterion of the wave function $\langle \psi | \psi \rangle = 1$. The beauty of the density matrix formalism is that the ensemble average of the expectation value of any operator can be calculated regardless of the choice of the basis set $\{\phi_i\}$.

In kinetic NMR studies one is interested in changes in the magnetization as a function of time. As $\vec{I}$ is independent of time, only the time-dependence of ρ is of importance, i.e.

$$\frac{d\text{Tr}(\rho \vec{I})}{dt} = \text{Tr} \left(\frac{d\rho}{dt} \vec{I} \right) \quad (4)$$

By use of the time-dependent Schrödinger equation²⁸ and the introduction of damping terms to take into account relaxation and chemical exchange, the equation of motion may be expressed as²²⁻²⁴

$$\frac{d\rho}{dt} = i [\rho, \mathcal{H}] + \Gamma(\rho) \quad (\text{atomic units}) \quad (5)$$

$[\rho, \mathcal{H}]$ denotes the commutator of the density operator and the Hamiltonian of the spin system. $\Gamma(\rho)$ is the dynamic term and, in the basis formed by the eigenfunctions of $\mathcal{H}$, is composed of the following three terms:

$$\Gamma(\rho) = -\frac{\rho_D - \rho^0}{T_1} - \frac{\rho_{OD}}{T_2} + \frac{d\rho_{\text{exchange}}}{dt} \quad (6)$$

ρ_D represents the diagonal and ρ_{OD} the off-diagonal elements of ρ . ρ^0 is the equilibrium density operator and T_1 and T_2 are the relaxation times longitudinal and transverse to the magnetic field B_0 . We shall now analyze the terms in equation (6) in some detail for the two different techniques used in the present investigation to obtain rate constants.

Line-shape treatment

The experiment which makes possible an observation of an NMR line-shape of nuclei in a molecule can be carried out in two different ways, either by varying the frequency $\omega_1 = \gamma B_1$ for a fixed magnetic field B_0 , or alternatively (but equivalently) by keeping ω_1 constant and varying the magnetic field B_0 . If the stimulating B_1 field is weak in the passage of the NMR lines, this implies that the diagonal components of the density matrix, ρ_D , will never be far from equilibrium and the first term in equation (6) vanishes.²⁹ Consequently, the only relaxation term which under these conditions can affect the line-shape is that in which T_2 is involved.

In intramolecular two-site exchanges, the exchange term, $\frac{d\rho_{\text{exchange}}}{dt}$, may simply be evaluated by considering changes in spin functions before and after an exchange event, if we also require that all spins of one molecular species interconvert with spins of another molecular species. Following Kaplan^{22,23} and Alexander²⁴, we can write equation (5) as

$$\frac{d\rho}{dt} = i[\rho, \mathcal{H}] - \frac{\rho}{T_2} + \frac{R\rho R^{-1} - \rho}{\tau} \quad (7)$$

τ is the mean lifetime of the nucleus (or nuclei) in the appropriate sites and R is a reorganization (exchange) operator whose matrix elements are functions of the chemical shifts and coupling constants,²² if eigenfunctions are used.

In the slow passage of the NMR lines the system is at a quasistationary equilibrium, which means that $\frac{d\rho}{dt}=0$, and the theoretical absorption spectrum is obtained directly as the sum of the imaginary parts of the density matrix which can give rise to a transition. The same information can in principle be obtained from the real part of the density matrix, which gives a dispersion spectrum. In the present investigations (see, for example, paper I) equation (7) has been solved for the coupled AB case to take into account up to three overlapping spectra.

In intermolecular rate processes or complicated exchanges where coupled nuclei exchange among several sites, the exchange term is quite tedious to calculate. An elegant method, called permutation of indices, has recently been developed by Kaplan and Fraenkel²⁹ for simplifying this evaluation. The elegance of this method lies in the choice of basis functions instead of eigenfunctions, by means of which the previous need to define R is by-passed. The exchange term is obtained directly by relabelling the ρ 's according to the reorganization process and permuting the basis function indices. Several examples for different kinds of exchanges are presented by these authors.

We have indirectly utilized this method (paper II) in the study of the temperature-dependence of the 4- and 6-methylene proton signals in 1,3-dibromo-2,4,6-trineopentyl-5-nitrobenzene (Im), which as

correctly assign the 4- and 6-methylene proton AB spectra of rotamers A and C in the analysis of spectra. (The 4-methylene protons in rotamer A are magnetically equivalent with the 6-methylene protons in rotamer C.) Note, however, that the interconversion $A \rightarrow B$ can not be distinguished from that of $A \rightarrow D$. More details are given in paper II together with the complete density matrix equations, expressed in explicit form.

Rate constants obtained by use of a double resonance technique

In line-shape treatment of spectra there are always problems of extracting reliable T_2 values in a temperature range where τ and T_2 are interdependent. It is possible to circumvent these difficulties by use of a double resonance technique, which was first developed by Forsén and Hoffman.³⁰⁻³² The method makes use of the fact that the saturation of all nuclear transitions in sites $\underline{t}$, $\underline{u}$, $\underline{v}$, ..., which are all connected by exchange to a nuclear resonance in site $\underline{s}$, reduces the z-magnetization in site $\underline{s}$ to a new equilibrium value. The phenomenon has been theoretically described by the McConnell formulation.²⁰

The first application of this technique to coupled AB spin systems is presented in paper III. The validity of the extension of the method can be established if we focus our attention on the diagonal components of ρ (cf. eq. (6)). These components are namely responsible for the populations³³ and thus determine the intensities. For simplicity we assume that the spectrum at slow interconversion rates consists of two AB spectra which at faster interconversions become a single AB spectrum. The exchange term (see eq. (7)) can easily be evaluated if we choose basis functions, but in this representation the commutator $[\rho, \mathcal{H}]$ is non-zero. To obtain an equation of form similar to that given by Forsén and Hoffman,^{30,31} normalized spin functions for each AB system must be used for which ρ and $\mathcal{H}$ commute.

These are given by³⁴

$$\begin{aligned}
 |1\rangle^S &= \alpha\alpha \\
 |2\rangle^S &= (1+Q_S^2)^{-1/2} [\beta\alpha - Q_S \alpha\beta] \\
 |3\rangle^S &= (1+Q_S^2)^{-1/2} [\alpha\beta + Q_S \beta\alpha] \\
 |4\rangle^S &= \beta\beta
 \end{aligned} \tag{8}$$

where s denotes the two different sites (I and II) and $Q_S = f(J_{AB}^S, (\omega_A - \omega_B)^S)$. In this representation the exchange term is somewhat more complicated, and if we call R the exchange operator, we can define a reorganization matrix with the property $RR^{-1} = I$ in the following way:

$$\begin{aligned}
 R |1\rangle^I &= |1\rangle^{II} \\
 R |2\rangle^I &= \lambda |2\rangle^{II} + \sqrt{1-\lambda^2} |3\rangle^{II} \\
 R |3\rangle^I &= \lambda |3\rangle^{II} - \sqrt{1-\lambda^2} |2\rangle^{II} \\
 R |4\rangle^I &= |4\rangle^{II}
 \end{aligned} \tag{9}$$

λ , the mixing coefficient, is obtained by expanding $|2\rangle^I$ or $|3\rangle^I$ in linear combinations of $|2\rangle^{II}$ and $|3\rangle^{II}$.

The intensity of the $k \rightarrow l$ transition in system I is proportional to the difference $\rho_{kk} - \rho_{ll}$. The time-dependence of this quantity is now given by

$$\begin{aligned}
 \frac{d}{dt}(\rho_{kk} - \rho_{ll})^I &= \frac{(\rho_{kk}^0 - \rho_{ll}^0)^I}{\tau_{kl}^I} - \frac{(\rho_{kk} - \rho_{ll})^I}{\tau_{kl}^I} - \frac{(\rho_{kk} - \rho_{ll})^I}{\tau_{I \rightarrow II}} + \\
 &+ \frac{(\rho_{nn} - \rho_{mm})^{II}}{\tau_{II \rightarrow I}} - (1 - \lambda^2) \frac{(\rho_{oo} - \rho_{mm})^{II}}{\tau_{II \rightarrow I}}
 \end{aligned} \tag{10}$$

ρ_{nn}, ρ_{mm} and ρ_{oo} are appropriate diagonal components of ρ .

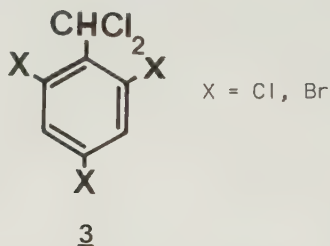
The diagonal component ρ_{nn} is equal to ρ_{mm} if we saturate the $n \rightarrow m$ transition in system II. If $\lambda=1$, which implies that the two systems have the same strength of coupling ($J_{AB}/(\omega_A - \omega_B)$)³⁵ and are only shifted with respect to each other, the solution of equation (10) is trivial under the conditions $\rho_{nn} = \rho_{mm}$. Moreover, if first order conditions exist in both systems (i.e. $J_{AB} \ll (\omega_A - \omega_B)$ or $J_{AB} \gg (\omega_A - \omega_B)$), or if $J_{AB} \approx (\omega_A - \omega_B)$, λ is approximately equal to 1 and the evaluation of $(\rho_{kk} - \rho_{ll})^I$ as a function of time is obtained by neglecting the last term.

This equation has been applied to the study of the temperature dependence of the methylene proton line-shape of 1,3-dibromo-2,4,6-trineopentyl-5-nitrobenzene (paper III) at moderately fast inter-conversion rates. The rotation of the 2-neopentyl group (between the bromines) in this compound was sufficiently slow in the temperature range -16-29°C to not contribute to the line width of the 4- and 6-methylene proton signals, and only one rate constant is thus involved in the changes of the line-shape. The mixing coefficient was approximately equal to 1, which made for a rather simple interpretation of the time-dependent decrease of the signal height investigated upon instantaneous saturation of the corresponding exchanging line.

The double resonance method is a good complement to the line-shape method, because slower interconversion rates^{31,32} ($\sim 0.1-1 \text{ sec}^{-1}$) can be studied. Unfortunately, the experimental conditions in the two studies of compound Im were different and the data from the experiments could thus not be combined to obtain activation parameters over a larger temperature interval.

DISCUSSION OF BARRIER HEIGHTS

In discussions of rotational barriers it is of importance to know the structural details of initial and transition state for the interconversion process. Quantum mechanical calculations of CNDO or ab initio type³⁶ give in general good results, but they can only be performed on small molecules. However, classical energy calculations of the Westheimer type³⁷ on larger molecules reproduce experimental barriers surprisingly well, if they are predominantly determined by steric factors. For example, recent calculations on 2,4,6-trisubstituted benzalchlorides (3) by Peeling, Ernst and



Schaefer³⁸ gave valuable information about the transition state. They found that the energy maximum was represented by a conformation in which the benzylic proton is perpendicular to the ring plane and not (as previously assumed³⁹ or roughly estimated⁴⁰) that in which one chlorine eclipses an ortho substituent.

At present, when such calculations have not been performed on our molecules, it is realistic to assume that the transition state is a conformation in which the slowly rotating neopentyl group is in the plane of the aromatic ring. The initial state in the symmetrically 2,4-disubstituted compounds is taken as a conformation in which the neopentyl group is perpendicular to the ring plane. This may not necessarily be true in the unsymmetrically substituted compounds and not even in a symmetrically tri-substituted 1,3,5-trineopentylbenzene (papers II and IV) if all rotations around sp^2-sp^3 bonds are frozen.

For the trineopentylbenzene compounds the entropies of activation, which will be further discussed below, are close to zero, and consequently, barrier heights are estimated from $\Delta G^\ddagger$ values, calculated from absolute reaction rate theory⁴¹ with the transmission coefficient equal to 1.⁴²

Halogen-and methyl-substituted compounds

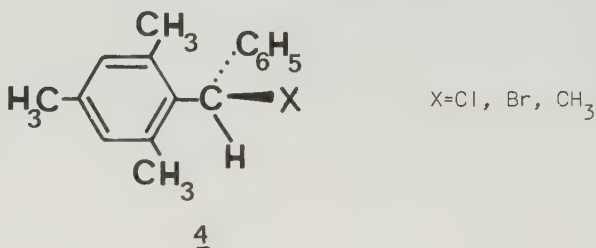
In the 2,4-dihalo-substituted compounds (Ia-g) the rotational barrier was found to be almost invariant with respect to the larger substituent ortho to the slowly rotating 3-neopentyl group (see papers I and II). This means that the rotations are primarily past the smaller halogen substituent provided the ortho substituents are not of equal or comparable magnitude.

It is realistic to assume that barriers to internal rotation in halo- or methyl-substituted trineopentylbenzenes are primarily steric in origin and to a large extent determined by the non-bonded interaction between one substituent and the t-butyl moiety of the slowly rotating neopentyl group. When the substituent grows larger the molecule is exposed to increased interactions, and large changes in geometry (bending and twisting) from molecule to molecule can also exist. However, in the trineopentylbenzenes, the substituents are buttressed by neopentyl groups and it is far from obvious if energy contributions of this kind are of importance for the height of the barrier. If energies due to bending are neglected, we have an excellent opportunity to utilize rotational barriers as a quantitative measure of relative "effective sizes" of substituents.

The size of a methyl group in the trineopentylbenzene series was found to be between that of a chlorine and a bromine (paper V), which is in accordance with previously reported results⁴³ for methyl and bromine deduced from comparisons of deuterium isotope effects in nitrations of compounds Ib and Ih. However, a methyl group can not be

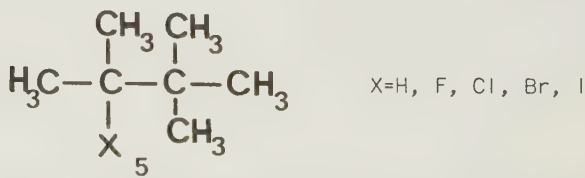
treated as a spherically or cylindrically symmetrical substituent such as a proton or a halogen (see paper V).

Work as early as 1932 on the configurational inversion of two series of biphenyls by Adams and coworkers⁴⁴ allowed the establishment of "relative interference effects" in the order $\text{Cl} < \text{CH}_3 < \text{Br}$. Results from NMR studies on α -substituted benzylmesitylenes (4)⁴⁵ indicated



that $\text{CH}_3 \approx \text{Cl} < \text{Br}$, whereas the steric substituent constant, E_s , introduced by Taft,⁴⁶ revealed the order $\text{Cl} < \text{Br} \approx \text{CH}_3$. Thus the placement of a methyl group in relation to a chlorine and a bromine in size is apparently not independent of the molecular system studied.

In the trineopentylbenzene series the rotational barriers cover a range from 5.4 kcal/mol for the passage of an aromatic proton by a neopentyl group to 18.8 kcal/mol for a similar passage of an iodine. Anderson and Pearson⁴⁷ have recently reported results from a series of halogen-substituted ethanes (5) with free energies of activation



between 7-11 kcal/mol. Although there may be factors other than steric responsible for the barriers in the ethanes, these are in our opinion at least comparable from molecule to molecule. It was thus of interest

to try to correlate the $\Delta\Delta G^*$ ($= \Delta G_X^* - \Delta G_H^*$, $X=F, Cl, Br, I$) values for corresponding substituents in the trineopentylbenzenes with those in the ethanes. A reasonably good straight line (correlation coefficient 0.991) could be drawn, which indicates that a linear free-energy relationship exists. However, the demands on such a free-energy relation are quite restrictive (see paper V or ref. 48) and without further examples of compounds with barriers covering the same extensive substituent range it seems to be too speculative to draw any general conclusions.

Nitro-substituted compounds

In some π -systems the energy associated with non-bonded interactions can be lowered at the expense of a decreased delocalization of electrons (steric inhibition of resonance). It is difficult to determine these effects separately, and consequently, the interpretation of barriers to internal rotation in compounds with resonance-stabilizing substituents such as NO_2 , NH_2 , $COOH$ or COR is not entirely straightforward.

The barrier to rotation past a nitro group in 1,3,5-trineopentyl-2,4-dinitrobenzene (1j) is lower than that due to a bromine in the dibromo compound (1b), but the "effective size" of a nitro group in this system is probably not correctly represented by $\Delta G_{298}^* = 13.3$ kcal/mol (see paper II). The value at 298°K obtained from the bromonitro compound (1k) is 14.4 ± 0.1 kcal/mol. Assume for the moment that the rotations primarily occur past the nitro group in the bromonitro compound. The difference in barriers between 1j and 1k can then be ascribed to resonance stabilization of the transition state in the dinitro compound by the nitro group that is not in steric contact with the t-butyl group during the rotation. The resonance effect from the cylindrically symmetric bromine is assumed to be the same in the initial and transition states.

However, it is not immediately evident that the 3-neopentyl group in 1k rotates predominantly past the nitro group. The barrier to rotation past the bromine in this compound may be lower than 16.6 kcal/mol, as obtained from 1e, because the transition state for such a rotation can be resonance stabilized by the nitro group. The observed barrier of 14.4 kcal/mol would then to a first approximation represent a resonance energy contribution of 2.2 kcal/mol for the nitro group. (It is appropriate to mention in this context that the internal rotational barrier in nitrobenzene is about 3 kcal/mol, as determined by microwave studies.⁴⁹) The barrier (ΔG_{298}^*) in 1k was however unaffected by a replacement of a bromine for an iodine (i.e. compound 1l). The possibility that in the bromonitro compound (1k) rotations may occur to about the same extent past both substituents with comparable barriers can thus be ruled out, because it would result in a ΔG^* value lower than 14.4 kcal/mol. (Equal barriers for the rotations past both substituents give a value of 14.0 kcal/mol at 298°K since $RT \ln 2 \sim 0.4$ kcal/mol; see for example paper 1, where symmetry factors are discussed.)

In 1,3-dibromo-2,4,6-trineopentyl-5-nitrobenzene (1m), we were able to evaluate two nitro-neopentyl barriers (14.3 ± 0.1 and 14.6 ± 0.1 kcal/mol) due to the existence of three rotamers. If we assume that the nitro group in rotamer B (or D) is nearly perpendicular to the ring plane in both initial and transition states, the barrier of 14.3 kcal/mol for the B (D) $\rightarrow$ A ($\equiv$ B (D) $\rightarrow$ C) conversion is then solely steric in origin. Support for the suggested initial state conformation has been obtained from NMR spectra of this compound (paper 11). The "effective size" of the nitro group in the 1,3,5-trineopentylbenzene system obtained from this compound and from compounds 1k and 1l is thus well represented by a ΔG^* value of about 14.2-14.5 kcal/mol.

DISCUSSION OF ENTROPIES OF ACTIVATION

ΔS^* values for the restricted rotation of the 3-neopentyl group in as many as 9 dihalo- and/or alkyl-substituted 1,3,5-trineopentylbenzenes cover a narrow range close to zero if realistic error limits⁵⁰ of around ± 3 cal/mol $^{\circ}\text{K}$ are assumed. This is perhaps unexpected in view of results on other molecules where rotational barriers also originate in an increased steric interaction. Schaefer and coworkers^{39,51,52} have found negative entropies of activation in studies on the restricted rotation around the $\text{sp}^2\text{-sp}^3$ bond in halogen-substituted benzalchlorides (3). The dineopentylbenzene compound (2), discussed above, has recently been reinvestigated (see paper V) and shown to give $\Delta S^* = -11.5 \pm 2.1$ cal/mol $^{\circ}\text{K}$. Negative entropies have also been reported by Reuvers *et al.*⁵³ in studies of 2,6-di-substituted neopentylbenzenes, but in these molecules with ortho substituents such as COR and CO₂R the barriers are most probably not solely steric in origin. Other examples of interest in this context are results from racemization studies of substituted biaryls, which also indicate negative entropies.⁵⁴

In the trineopentylbenzene studies chloroform-*d* was used nearly exclusively as solvent, and it might be of importance in the interpretation of the entropy term. A complex between the solvent and the aromatic ring may exist in either the initial or the transition state. However, NMR studies^{55,56} of the association complex between benzene and chloroform reveal that quite small changes in energy (< 0.1 kcal/mol) occur during formation or rupture of the complex.

Another origin of the entropy term, although less probable for our molecules, may be the existence of a temperature dependence in the ΔH^* value. An effect of this kind results in an incorrect ΔS^* term due to the presumption of a temperature independent enthalpy term in the treatment of rate data. As discussed by Dahlquist and Forsén⁵⁷,

it would be nearly impossible to detect a temperature dependence in the enthalpy of activation in NMR studies where a rather narrow temperature interval is investigated. The origin of ΔS^* in our compounds would more likely be found in other inherent properties of the molecule.

The rotation of one neopentyl group past an ortho substituent involves not only a change in the dihedral angle between the aromatic ring and the plane through the neopentyl group, but also a change in the orientations of the methyl groups in the neopentyl group in question (i.e. a "gear effect"⁵⁸). Losses of vibrational degrees of freedom in the transition state are of minor importance⁵⁹ for the magnitude of ΔS^* , because almost all molecules are in the lowest vibrational level. On the contrary, it is expected that the transition state would be more rigid with respect to the rotational freedom of the t-butyl group. Using the expression for the rotational contribution (see equation 11 and 12) to the entropy in statistical mechanics, a value of 7 cal/mol °K at 300 °K can be calculated⁶⁰ for a freely rotating t-butyl group. In equations 11 and 12, Q is the partition

$$S = R \left(\ln Q - \frac{1}{QT} \frac{\partial Q}{\partial \left(\frac{1}{T} \right)} \right) \quad (11)$$

$$Q = \frac{(8\pi^3 I k T)^{1/2}}{nh} \quad (12)$$

function for a rigid rotor, I is the reduced moment of inertia and n is the symmetry number.

However, it is clear from model studies of 1,3,5-trineopentylbenzenes that the t-butyl group rotating past the substituent is not completely locked in the transition state, but nevertheless a slightly negative value of ΔS^* would be expected.

In the case of compound 2 it is not quite obvious from model studies if the transition state is analogous to that in the trineopentylbenzenes. In paper V we have discussed the possibility that the maximum in the energy profile is instead reached after the neopentyl group has passed the methyl group, which would imply a rather rigid conformation with losses of rotational degrees of freedom of methyl and/or t-butyl groups as discussed above. Hence, the appearance of a large negative entropy in this case seems rather reasonable.

FINAL COMMENTS

In this thesis I have presented results from NMR studies on 1,3,5-trineopentylbenzene compounds, which, as shown, can give rise to rather complicated spectra. In my opinion, it is rather an advantage than a disadvantage to investigate complicated spectra (if they can be analyzed in detail) because more intimate details about the behaviour of the molecule can be obtained than if molecules are "simplified" for the analysis of spectra by for example replacement of protons by deuterium. Signals which are poorly resolved at 60 MHz are in general well separated if spectrometers with higher frequencies are utilized. However, 220, 300 and even 500 MHz spectrometers are quite rare and require superconducting solenoids which at present are rather expensive.

A new inroad to stereochemical or conformational studies by means of high-resolution NMR has emerged in recent years through developments in the use of the Fourier transform technique, which allows an easier detection of the isotope ^{13}C (natural abundance 1.1 %). The total range of ^{13}C shielding is a factor of about 60 times greater than that of ^1H shielding, which thus may offer new possibilities for solving stereochemical and conformational problems.

ACKNOWLEDGEMENTS

I wish to express my sincere thanks to Dr. Robert E. Carter for introducing me to this research, for skilful linguistic criticism and for enthusiastic support throughout the work presented in this thesis. Thanks are also due to Professor Börje Wickberg for his kind interest in this work and for partial time off from other duties in the latter phase of the thesis work. I am especially grateful for the indispensable aid of Mrs. Gunnel Torstensson, who prepared all versions of the papers.

In my thanks I also wish to include all my colleagues, especially Dr. Torbjörn Drakenberg, Dr. Per Martinson and Dr. Kåre Olsson for enjoyable collaboration and Dr. Håkan Wennerström for many fruitful discussions concerning the theoretical problems.

Partial financial support by a scholarship from the Bengt Lundquist Memorial Foundation is gratefully acknowledged.

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